

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

18 December 1998 (18.12.98)

International application No.

PCT/US98/08798

Applicant's or agent's file reference

ISIS-2988

International filing date (day/month/year)

30 April 1998 (30.04.98)

Priority date (day/month/year)

30 April 1997 (30.04.97)

Applicant

DEAN, Nicholas, M. et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

25 November 1998 (25.11.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

P. Regis

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

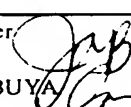
REC'D 03 AUG 1999

WIPO PCT

Applicant's or agent's file reference ISIS-2988	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/08798	International filing date (day/month/year) 30 APRIL 1998	Priority date (day/month/year) 30 APRIL 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report
 - II ☐ Priority
 - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 25 NOVEMBER 1998	Date of completion of this report 17 JUNE 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer:  MARK SHIBUYA Telephone No. (703) 308-0196 JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/08798

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

☒ the international application as originally filed.

☒ the description, pages 1-38 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of _____.

pages _____ , filed with the letter of _____.

☒ the claims, Nos. NONE , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. 1, 8, 10-18, , filed with the letter of 24 May 1999

27-33

Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/fig 1-8 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of _____.

sheets/fig _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. 2-7, 9 and 19-26 .

☒ the drawings, sheets/fig NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO
Inventive Step (IS)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO
Industrial Applicability (IA)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 8 and 10 lack novelty under PCT Article 33(2) as being anticipated by Hanecak et al.

Claims 11-14, 16-18 27 and 28-33 lack an inventive step under PCT Article 33(3) as being obvious over Hanecak et al. in view of Lesnik et al., Milligan et al., Manoharan et al. (Tetrahedron Letters 26, 3651-3654), Manoharan et al. (Nucleosides & Nucleotides 14, 969-973), van Berge-Henegouwen et al., Agrawal et al. and Vlassov et al.

Hanecak et al., at page 5204, paragraph 3, teaches a 2'-alkoxyalkoxy modification that is a 2'-methoxyethoxy modification.

Lesnik et al., at page 7834, Table II and page 7835, teach modified oligonucleotides comprising at least one 2' sugar modification, that is 2'-O-propyl. Milligan et al., at page 1923, Table 1, 1925 and pages 1931-1933, Figure 3, teach modified oligonucleotide comprising at least one heteroatomic backbone modification, modifications to the 2' sugar, including 2'-O-methyl modifications, a 5-methylcytidine nucleotide, colloidal dispersion systems and penetration enhancers. Manoharan et al. (Tetrahedron Letters 26, 3651-3654), teach bile salts. Manoharan et al. (Nucleosides & Nucleotides 14, 969-973), teach fatty acids. van Berge-Henegouwen et al., at pages 305-308 teach the rapid absorption of chenodeoxycholic acid (CDCA). Agrawal et al., at page 572, paragraphs 2-3, teach methods of enhancing bioavailability of ODN, wherein said oligonucleotides are administered into the alimentary canal by oral administration and said oligonucleotide has a phosphorothioate backbone modification and a 2'-O-alkyl sugar modification. Vlassov et al. at page 271 teach the methods administering oligonucleotides into the alimentary tract.

It would have been prima facie obvious at the time the invention was made to one of ordinary skill in the art to make a modified oligonucleotide comprising at least one heteroatomic backbone modification, and a 2'-alkoxyalkoxy modification wherein (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/08798

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): C12Q 1/68; C12N 15/00, 15/63; 5/06; C07H 21/00, 21/04; A61K 48/00 and US Cl.: 435/6, 91.1, 172.3, 320.1, 353; 536/23.1, 24.31, 24.5; 514/44

V. 1. REASONED STATEMENTS:

The report as to Novelty was positive (YES) with respect to claims 11-18, 27-33.

The report as to Novelty was negative (NO) with respect to claims 1, 8, 10.

The report as to Inventive Step was positive (YES) with respect to claims 15.

The report as to Inventive Step was negative (NO) with respect to claims 1, 8, 10, 11-14, 16-18, 27-33.

The report as to Industrial Applicability was positive (YES) with respect to claims 1, 8, 10-18, 27-33.

The report as to Industrial Applicability was negative (NO) with respect to claims none.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

said alkoxyalkoxy modification is 2'-methoxyethoxy, or at least one 2' sugar modification, in a colloidal dispersion system, or a penetration enhancer comprising a bile salt that is CDCA or a fatty acid in order to increase uptake and stability of antisense oligonucleotides as taught by the aforementioned references and to use methods of enhancing bioavailability of modified oligonucleotide (ODN) in the claimed compositions during or after administration in the alimentary canal. One of ordinary skill in the art would have had a reasonable expectation of success in making the modified oligonucleotide compositions, including the colloidal dispersion systems and penetration enhancers, because Milligan et al. teach oligonucleotides comprising heteroatomic backbone modifications and sugar modification in both phosphorothioate backbone and 2' sugar modifications in compositions comprising colloidal dispersion systems and penetration enhancers, and absence evidence to the contrary, bile salts, CDCA and fatty acids could be substituted for the fatty acids, and to use methods of enhancing bioavailability as taught by Agrawal et al. and Vlassov et al.

----- NEW CITATIONS -----

NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08798**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 91.1, 172.3, 320.1, 353; 536/23.1, 24.31, 24.5; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, BIOSIS, MEDLINE, DERWENT WPI, CA SEARCH, DERWENT BIOTECH ABS, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	AGRAWAL, S. et al. Absorption, Tissue Distribution and In Vivo Stability in Rats of a Hybrid Antisense Oligonucleotide Following Oral Administration. Biochem Pharmacol. 1995, Vol. 50, No. 4, pages 571-576, see entire document.	1, 3-6, 10, 19, 21-24 ----- 2, 7-9, 11-18, 20, 24-27
X -- Y	VLASSOV, V.V. et al. Penetration of Oligonucleotides Into Mouse Organism Through Mucosa and Skin. FEBS Letters. August 1993, Vol. 327, No. 3, pages 271-274, see entire document.	1, 3, 10, 19, 27 ----- 2, 4-9, 11-18, 20-26
Y	MILLIGAN, J.F. et al. Current Concepts in Antisense Drug Design. J. Medicinal Chemistry. 09 July 1993, Vol. 36, No 14, pages 1923-1937, especially pages 1923, 1924, 1931, 1932, 1933.	2, 4-10, 12, 17, 18, 20-26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

23 MAY 1998

Date of mailing of the international search report

19 AUG 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MARK SHIBUYA, PHD

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08798

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ROJANASAKUL, Y. Antisense Oligonucleotide Therapeutics: Drug Delivery and Targeting. Advanced Drug Delivery Reviews. 1996, Vol. 18, pages 115-131, especially pages 121-122.	11, 12
Y	HANCAK, R. et al. Antisense Oligonucleotide Inhibition of Hepatitis C Virus Gene Expression in Transformed Hepatocytes. J. Virology. August 1996, Vol. 70, No. 8, pages 5203-5212, especially pages 5203, 5210-5211.	2, 19, 20
Y	LESNIK, E.A., et al. Oligodeoxynucleotides Containing 2'-O-Modified Adenosine: Synthesis and Effects on Stability of DNA:RNA Duplexes. Biochemistry. 1993, Vol. 32, No. 30, pages 7832-7838, see entire document.	5- 8, 18, 21- 25
Y	MANOHARAN, M. et al. Oligonucleotide Conjugates: Alteration of the Pharmacokinetic Properties of Antisense Agents. Nucleosides & Nucleotides. 1995, Vol. 14, No. 3-5, pages 969-973, see entire document.	10-14, 16
Y	van BERGE-HENEGOUWEN et al. Pharmacology of Chenodeoxycholic Acid. II. Absorption and Metabolism. Gastroenterology. August 1977, Vol. 73, pages 300-309, see entire document.	10-14, 16
Y	MANOHARAN, M. et al. Lipidic Nucleic Acids. Tetrahedron Letters. 1995, Vol. 36, No. 21, pages 3651-3654, see entire document.	13, 15, 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08798

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08798

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C12Q 1/68; C12N 15/00, 15/63; 5/06; C07H 21/00, 21/04; A61K 48/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/6, 91.1, 172.3, 320.1, 353; 536/23.1, 24.31, 24.5; 514/44